IB

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To: JEFFRY S. MANN
TOWNSEND AND TOWNSEND AND CREW LLP
TWO EMBARCADERO CENTER
8TH FLOOR
SAN FRANCISCO, CALIFORNIA 94111-3834

PCT

WRITTEN OPINION

(PCT Rule 66)

Date of Mailing *(day/month/year)*	14 MAY 2002
Applicant's or agent's file reference 18062G-32-1P	REPLY DUE 7-14-02 within TWO months from the above date of mailing
International application No. PCT/US01/17265	International filing date *(day/month/year)* 25 MAY 2001
Priority date *(day/month/year)* 02 JUNE 2000	

International Patent Classification (IPC) or both national classification and IPC
Please See Supplemental Sheet.

Applicant
REGENTS OF THE UNIVERSITY OF CALIFORNIA

1. This written opinion is the first (first, etc.) drawn by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

- I [X] Basis of the opinion
- II [ ] Priority
- III [ ] Non-establishment of opinion with regard to novelty, inventive step or industrial applicability
- IV [ ] Lack of unity of invention
- V [X] Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI [ ] Certain documents cited
- VII [X] Certain defects in the international application
- VIII [X] Certain observations on the international application

3. The applicant is hereby invited to reply to this opinion.

When? See the time limit indicated above. ~~The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).~~

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 *bis*.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 02 OCTOBER 2002

Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer JEFFREY E. RUSSEL Telephone No. (703) 308-0196
Facsimile No. (703) 305-3230	

Form PCT/IPEA/408 (cover sheet) (July 1998)*

RESPONSE 7-14-02 KAD
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VI	[ ]	Certain documents cited
VII	[X]	Certain defects in the international application
VIII	[X]	Certain observations on the international application

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WRITTEN OPINION

International application No.
PCT/US01/17265

I. Basis of the opinion

1. With regard to the **elements** of the international application:*

[X] the international application as originally filed

[X] the description:
pages 1-62, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____

[X] the claims:
pages 63-79, as originally filed
pages NONE, as amended (together with any statement) under Article 19
pages NONE, filed with the demand
pages NONE, filed with the letter of _____

[X] the drawings:
pages 1-15, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____

[X] the sequence listing part of the description:
pages NONE, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

[ ] the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

[ ] the language of publication of the international application (under Rule 48.3(b)).

[ ] the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the written opinion was drawn on the basis of the sequence listing:

[ ] contained in the international application in printed form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readable form.

[ ] The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] The statement that the information recorded in computer readable form is identical to the writen sequence listing has been furnished.

4. [X] The amendments have resulted in the cancellation of:

[X] the description, pages NONE

[X] the claims, Nos. NONE

[X] the drawings, sheets/~~fig~~ NONE

5. [ ] This opinion has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed".*

WRITTEN OPINION

International application No.
PCT/US01/17265

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. statement

Novelty (N)	Claims	(Please See supplemental sheet)	YES
	Claims	(Please See supplemental sheet)	NO
Inventive Step (IS)	Claims	(Please See supplemental sheet)	YES
	Claims	(Please See supplemental sheet)	NO
Industrial Applicability (IA)	Claims	(Please See supplemental sheet)	YES
	Claims	(Please See supplemental sheet)	NO

2. citations and explanations

Claims 16, 18, 19, 21-26, 29, 32, 35, 36, 40, 41, 43, 44, 46, 48, 51, 53, 60-63, 66, and 69-72 lack novelty under PCT Article 33(2) as being anticipated by Del Nery et al. Del Nery et al teach a peptidyl-MCA library used to characterize the substrate specificity of the major cysteine protease from the parasitic protozoan Trypanosoma cruzi. Fluorescence is measured in a spectrofluorimeter. See, e.g., the Abstract, page 429, column 1, second paragraph; page 430, column 2, last paragraph, and page 431 and Table 3. The peptidyl-MCA substrates correspond to Applicant's peptides R-P in which R^{1o} is absent and Y is methyl, and in which c=0. The peptides reported in Table 3 correspond to Applicant's peptide library, and the numerical results reported in Table 3 correspond to Applicants' database.

Claims 49, 50, 54-59, 64, 65, 67, and 68 lack an inventive step under PCT Article 33(3) as being obvious over Del Nery et al. Application of Del Nery et al is the same as in the above paragraph. Del Nery et al do not teach a peptide library comprising more than seven peptidyl-MCA substrates. It would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to form a library comprising more than seven peptidyl-MCA substrates, e.g., comprising at least 1,000,000 different peptidyl-MCA substrates, because peptide libraries comprising large numbers of peptides are well-known in the art, and because use of a larger peptidyl-MCA library will permit a more complete characterization of activity of cruzipain, which is disclosed to be desirable by Del Nery et al. Del Nery et al do not teach converting their database in table 3 into an electronic database and distributing it on a wide area network. It would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to convert the database of Del Nery et al into an electronic database and distributing it on a wide area network because converting data into electronic databases and distributing them on a wide area network is a conventional method for handling scientific data and which has the benefit of saving storage space in comparison to physical storage means and also has the benefit of permitting easier access to the database by the creator or by other interested (Continued on Supplemental Sheet.)

WRITTEN OPINION

International application No.
PCT/US01/17265

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

Claim 2 is objected to under PCT Rule 66.2(a)(iii) as containing the following defect(s) in the form or contents thereof: Claim 2 ends with a semicolon rather than with a period.

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Claims 60, 72, and 77 are objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 6 because the claims are indefinite for the following reason(s): In claim 60, it is not clear what is meant by "located", e.g., if this means a physical location, or if this means the peptide is modeled after a particular region of a substrate. Also, the claim is silent as to what the substrate is a substrate for. Claim 72 is unclear because there is already a step (c) in claim 61. Also, claim 72 appears to duplicate claim 62. There is no antecedent basis in the claims for the phrase "said active ester" in claim 77. It is possible that claim 77 should instead depend upon claim 76.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

TIME LIMIT:
The time limit set for response to a Written Opinion may not be extended. 37 CFR 1.484(d). Any response received after the expiration of the time limit set in the Written Opinion will not be considered in preparing the International Preliminary Examination Report.

CLASSIFICATION:
The International Patent Classification (IPC) and/or the National classification are as listed below:
IPC(7): C07D 311/02; C07K 1/04, 1/13; C08J 7/12; C12Q 1/04, 1/37; C01N 33/52; G06F 19/00 and US Cl.: 435/23, 24, 34; 525/50, 54.1, 54.11; 530/334, 345; 549/288; 702/22, 30

V. 1. REASONED STATEMENTS:
The opinion as to Novelty was positive (YES) with respect to claims 1-15, 17, 20, 28, 30, 31, 33, 34, 37-39, 45, 49, 50, 54-59, 64, 65, 67, 68, and 73-83
The opinion as to Novelty was negative (NO) with respect to claims 16, 18, 19, 21-27, 29, 32, 35, 36, 40-44, 46-48, 51-53, 60-63, 66, and 69-72.
The opinion as to Inventive Step was positive (YES) with respect to claims 1-15, 17, 20, 30, 31, 33, 34, 37-39, 45, and 73-83.
The opinion as to Inventive Step was negative (NO) with respect to claims 16, 18, 19, 21-29, 32, 35, 36, 40-44, and 46-72.
The opinion as to Industrial Applicability was positive (YES) with respect to claims 1-83.
The opinion as to Industrial Applicability was negative (NO) with respect to claims NONE.

V. 2. REASONED STATEMENTS - CITATIONS AND EXPLANATIONS (Continued):
'parties.

Claims 16, 18, 19, 21-24, 27, 29, 32, 35, 36, 40-44, 46, 47, 51-53, 60-63, 66, 69, and 72 lack novelty under PCT Article 33(2) as being anticipated by Sawada et al. Sawada et al teach a peptidyl-MCA library used to characterize the substrate specificity of spermosin and acrosin, which are trypsin-like proteases (i.e. are serine proteases) and are obtained from the animal H. roretzi, which is used as an animal model for studying the role of sperm proteases in fertilization. Fluorescence intensity is measured using a recorder. See, e.g., the Abstract; page 240, column 2, first full paragraph; page 241, column 2, first full paragraph; and page 242, Table 2. The peptidyl-MCA substrates correspond to Applicant's peptides R-P in which R^{20} is absent and Y is methyl, and in which c=0. The peptides reported in Table 2 correspond to Applicant's peptide library, and the numerical results reported in Table 2 correspond to Applicant's database.

Claims 28, 54-59, 64, 65, 67, and 68 lack an inventive step under PCT Article 33(3) as being obvious over Sawada et al. Application of Sawada et al is the same as in the above paragraph. Sawada et al do not teach characterizing the activity of human proteases using their peptidyl-MCA substrates. It would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to characterize the activity of human proteases using the peptidyl-MCA substrates of Sawada et al because Sawada et al disclose their H. roretzi proteases to be useful models for animal models and because it would be desirable to characterize the activity of human proteases in order to be able to study fertilization in humans. Sawada et al do not teach a peptide library comprising more than five peptidyl-MCA substrates. It would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to form a library comprising more than five peptidyl-MCA substrates, e.g., comprising at least 1,000,000 different peptidyl-MCA substrates, because peptide libraries comprising large numbers of peptides are well-known in the art, and because use of a larger peptidyl-MCA library will permit a more complete characterization of activity of spermosin and acrosin, which is disclosed to be desirable by Sawada et al. Sawada et al do not teach converting their database in table 2 into an electronic database and distributing it on a wide area network. It would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to convert the database of Sawada et al into an electronic database and distributing it on a wide area network because converting data into electronic databases and distributing them on a wide area network is a conventional method for handling scientific data and which has the benefit of saving storage space in comparison to physical storage means and also has the benefit of permitting easier access to the database by the creator or by other interested parties.

Claims 1-15, 17, 20, 30, 31, 33, 34, 37-39, 45, and 73-83 meet the criteria set out in PCT Article 33(2)-(3). With respect to Applicant's claims 1-15 and 73-83, the prior art of record does not teach or suggest fluorogenic moieties linked to a solid support and having the structure indicated in Applicant's claim 1. Accordingly, methods of making and using such materials are also novel and unobvious over the prior art of record. The prior art of record does not teach or suggest fluorogenic peptides having the particular structures recited in Applicant's claims 17, 20, 33, 34, and 37. With respect to instant claims

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

30 and 31, both Del Nery et al and Sawada et al are limited to determining the activity of enzymes per se, and do not suggest that enzymes present in intact microorganisms can be identified by their disclosed assays. With respect to instant claims 38, 39, and 45, neither Del Nery et al nor Sawada et al teach or suggest variations within their disclosed peptidyl-MCA substrates of the type required by these claims.

Claims 1-83 meet the criteria set out in PCT Article 33(4). The claimed invention would have been expected to have industrial applicability in assays for identifying and characterizing enzymes and microorganisms.

---------- NEW CITATIONS ----------

DEL NERY et al. Characterization of the substrate specificity of the major cysteine protease (cruzipain) from Trypanosoma cruzi using a portion-mixing combinatorial library and fluorogenic peptides. Biochemical Journal. 1997, Volume 323, pages 427-433, especially the Abstract, page 429, column 1, second paragraph, page 430, column 2, last paragraph, page 431, and Table 3.

SAWADA et al. Substrate Specificity of Ascidian Sperm Trypsin-Like Proteases, Spermosin and Acrosin. Molecular Reproduction And Development. 1996, Volume 45, pages 240-243, especially the Abstract, page 240, column 2, first full paragraph, page 241, column 2, first full paragraph, Table 2.